REMARKS

Claims 1-4 are pending in this application. Claim 4 is amended to recite "a purity suitable for use in a pharmaceutical composition", for additional clarity. Therefore, no new matter is introduced. Claims 5 and 7 are cancelled with out prejudice or disclaimer. Claims 6 and 8-14 are withdrawn by the examiner. The Office Action is discussed below:

Obviousness Rejection:

On pages 3-9 of the Office Action, the examiner has rejected claims 1-4 and alleged as being unpatentable over Hille *et al.* (US patent 5,705,186) in view of Gao *et al.* (US patent publication 2003/0050257) or Merrill *et al.* (US patent 5,593,695) or Berge *et al.* in view of Remington. According to the examiner, Hille *et al.* discloses transdermal compositions comprising morphine-6-glucuronide or its salts (see column 1, lines 45-55). Although Hille *et al.* mentions that pharmaceutically acceptable salts may be suitable for use, specifically discloses that the hydrochloride salt is preferred (see column 3, lines 22-25). Hille *et al.,* however, does not disclose a hydrobromide salt. In this context, applicants refer that preferred species that teach away from the claimed invention are indicative of non-obviousness and the absence of a suggestion to combine:

> A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.
>
> *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994) (emphasis added).

Applicants also refer the examiner to the dictates of the MPEP that:

> teachings of preferred species of a complex nature within a disclosed genus may motivate an artisan of ordinary skill to make similar complex species and thus teach away from making simple species within the genus. *Baird*, 16 F.3d at 382, 29 USPQ2d at 1552. See also *Jones*, 958 F.2d at 350, 21 USPQ2d at 1943 (disclosed salts of genus held not sufficiently similar in structure to render claimed species *prima facie* obvious).
>
> *See* MPEP § 2144.08 II(A)4(c) (Rev. 6, September 2007) at 2100-157-158.

In this case, Hille *et al.* mentions that the hydrochloride salt is preferred (see column 3, lines 22-25) and the examiner also admits that Hille *et al.* does not disclose a

hydrobromide salt of morphine-6-glucuronide. Thus, a person of ordinary skill, upon reading Hille *et al.*, would be discouraged from following a path to use a hydrobromide salt of morphine-6-glucuronide, as instantly claimed.

In order to assist the examiner further distinguishing the claimed invention from the cited references, applicants submit the following:

With regard to Gao *et al.*, the examiner states that this document discloses a number of glycosylated morphine derivatives, including 6-glucuronide adducts (citing page 1, paragraphs 0014-0021), and that pharmaceutically acceptable salts of these compounds include the bromide salts (citing paragraph 0037). However, there is no disclosure in paragraphs 0014-0021 of Gao *et al.* of 6-glucuronide adducts of morphine. The only glucuronides disclosed in these paragraphs are 3-glucuronide adducts of nordihydromorphine (paragraph 0019), nordihydroisomorphine (paragraph 0020), and norhydromorphone (paragraph 0020). Apart from reference to morphine-6-glucuronide at paragraph 0007 of the "Background of the invention", there appears to be no disclosure in Gao *et al.* of glucuronide adducts of morphine, and there is no disclosure of pharmaceutically acceptable salts of glucuronide adducts of morphine. There also appears to be no disclosure in Gao *et al.* of pharmaceutically acceptable salts of 6-glucuronide adducts of morphine derivatives. Paragraph 0037 of Gao *et al.* refers to pharmaceutically acceptable salts being a salt formed from an acid and the basic nitrogen group of one of the compounds of formula (I)-(V). None of the compounds of formula (I)-(V) are glucuronide adducts of morphine; they are glucose adducts of hydromorphone (I), dihydromorphine (IV), (V), or dihydroisomorphine (II), (III). Thus, there is no disclosure in Gao *et al.* that the hydrobromide is a pharmaceutically acceptable salt of a glucuronide adduct of morphine. Consequently, a combination of Hille *et al.* and Gao *et al.* does not provide the claimed subject matter, and the skilled person would not be led by the disclosure of Gao *et al.* to make the hydrobromide salt of M6G.

The examiner asserts that Remington discloses that it is typical and routine in the art to make and evaluate a number of different salt forms of a given drug, including the hydrobromide ion, in order to determine the optimal salt form for the desired application. This appears to be the examiner's interpretation of the disclosure of Remington. This document does not appear to contain any disclosure that it is routine to evaluate the hydrobromide salt form of a given drug. The hydrobromide salt is

simply referred to in Table 2 as a salt form marketed between 1983-1996. There is no disclosure in this document of the suitability of any of the salts for combination with M6G, nor that any particular salt forms compounds with improved stability. The examiner considers on the basis of the pKa and ClogP in Table 2 of Remington that hydrobromide is disclosed by this document to be a pharmaceutically acceptable counterion similar to hydrochloride. On this basis, the skilled person would have no motivation to substitute the hydrochloride salt with the hydrobromide salt because they would not expect that the hydrobromide salt would provide any advantageous properties compared with the hydrochloride salt.

Applicants have found that M6G.HBr is unexpectedly advantageous and possesses superior stability properties compared to M6G base and other M6G salts, including the hydrochloride salt (see specification page 1, lines 19-22, for example). The present application clearly demonstrates the increased stability of M6G.HBr compared with M6G.HCl (see specification, Examples 1 and 3, and Tables 1-4, for example). M6G.HBr also was found to be stable when subject to storage conditions of 25°C/60%RH and 40°C/75%RH for 3 months and 60°C for 1 month. M6G.HBr shows a very limited amount of degradation and no discoloration after storage at room temperature for six years. In contrast, M6G.HCl showed almost 10% unknown related substances after storage at room temperature for six years (see Table 1), and was the least stable of the salts tested at 40°C/75% humidity, showing the greatest level of degradation. The content of M6G.HCl was decreased to 69% (starting from about 82%) when storage at room temperature for six years (see specification, Example 1 at page 4, for example).

In this context, applicants invite the examiner to consider the MPEP, which states:

> A *prima facie* case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).
>
> *See* MPEP §2144.09 (VII) (Rev. 6, September 2007 at 2100-162).

In this case, the claimed hydrobromide salt of morphine-6-glucuronide (M6G.HBr) has unexpected superior physical properties. In particular, the claimed M6G.HBr has unexpectedly long stability compared to M6G base compound and other M6G salts (see page 1, paragraph 4 of the specification). Applicants also indicate that

there is no suggestion to the skilled person in the cited references to make a hydrobromide salt of M6G, nor any teaching that such a salt might have advantageous properties. Therefore, a mere disclosure in the art that "bromide ion is suitable as a counterion", as relied upon by the examiner, does not render the claimed invention obvious.

On pages 5-7 of the Office Action, the examiner has rejected claims 1-4 under U.S.C. 103(a) allegedly as being unpatentable over Hille *et al.* in view of Merrill *et al.* in view of Remington. Merrill *et al.* relates to morphine therapy, composition of matter and dosage form comprising morphine for administering the dosage form for delivering morphine to produce an analgesic effect (see col. 1, lines 35-47). Although morphine hydrobromide is listed as one "representative" of morphine, there is no teaching in Merrill *et al.* regarding any improved properties associated with the hydrobromide salt of morphine, nor any disclosure of M6G, nor any disclosure or suggestion to use a hydrobromide salt of M6G, as instantly claimed. Therefore, Merrill *et al.* does not disclose the claimed compound nor provides any suggestion to use a hydrobromide salt of the instantly claimed M6G-hydrobromide.

As discussed above, Merrill *et al.* and Remington do not rectify the deficiencies of Hille *et al.*, therefore, a combination of these references does not render the claimed invention obvious.

On pages 7-9 of the Office Action, the examiner has rejected claims 1-4 under U.S.C. 103(a) allegedly as being unpatentable over Hille *et al.* in view of Berge *et al.* in view of Remington. Berge *et al.* discloses in Table 1, page 2, a number of FDA-approved commercially marketed salts, including hydrobromide. However, there is no suggestion of the potential beneficial properties it may provide such as long-term stability, especially in combination with any specific base compound. It is clear from Table 1 of Berge *et al.* that the hydrobromide was an uncommon choice to be used as a salt of any compound (1.9% of the total number of anionic or cationic salts in use through 1974), which does not provide any motivation to the skilled artisan to use a hydrobromide salt opposed to hydrochloride salt having a use of 42.98% (see Table 1 of Berge *et al.*). Besides, the hydrochloride salt is stated to be by far the most frequent choice of the available anionic salt-forming radicals (42.98% use). Therefore, the skilled person would not have been motivated from the teaching of Berge *et al.* to substitute the hydrochloride salt with the hydrobromide salt. *See* MPEP § 2144.08

II(A)4(c) (Rev. 6, September 2007) at 2100-157-58. Nonetheless, as discussed above, Berge *et al.* or Remington does not disclose the instantly recited morphine-6-β-D-glucuronide (M6G) and nor do they rectify the deficiencies of Hille *et al.* Therefore, a combination of these references does not render the claimed invention obvious.

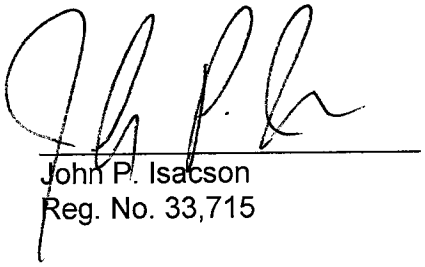
Moreover, none of the cited documents teaches or suggests that the hydrobromide salt of M6G would have advantageous properties, in particular increased long term stability, compared with M6G base and other M6G salts (including the hydrochloride salt). A mere disclosure in the art that the hydrobromide ion is a pharmaceutically acceptable counterion, as relied upon by the examiner, does not render the claimed invention obvious.

In view of the above, applicants submit that a *prima facie* case of obviousness has not been established by the examiner, accordingly, withdrawal of the obviousness rejection is solicited.

REQUEST

Applicants submit that claims 1-4 are in condition for allowance, and respectfully request favorable consideration to that effect. The examiner is invited to contact the undersigned at (202) 416-6800 should there be any questions.

Respectfully submitted,



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